

REMARKS/ARGUMENTS

Claims 1 and 4-12 are pending in the captioned application. The only remaining issue is whether the claims are obvious in view of a combination of references. Applicants respectfully request reconsideration and allowance of the claims in view of the following arguments.

Claims 1, 4-7, 11 and 12 stand rejected again under 35 U.S.C. §103(a) as being unpatentable over Hardin (US2003/0064366A1) in view of McGuigan (Methods Enzymol. 1993; 218:241-58). Applicants respectfully disagree.

The current invention relates to a method for increasing the rate of an enzyme catalyzed nucleoside monophosphate transfer to detect the activity of the enzyme or the terminal-phosphate-labeled nucleoside polyphosphate. The method is realized by the unexpected finding of Applicants that in the presence of manganese, the rate of enzyme catalyzed nucleoside monophosphate transfer from a terminal-phosphate-labeled nucleoside polyphosphate increases over the rate of a reaction in the absence of manganese.

Applicants submit that Hardin, as discussed by the Examiner, relates to a method that does includes an enzyme catalyzed nucleoside monophosphate transfer. Hardin also teaches gama-phosphate labeled ddNTP. However, Applicants submit that Hardin does not teach a reaction buffer comprising manganese. Further, there is no discussion about the rate of enzyme catalyzed nucleoside monophosphate transfer.

Applicants submit that the Examiner's analysis of McGuigan seems flawed. The Examiner states that McGuigan teaches that upon addition of manganese ions to a Sequenase reaction system, "the polymerase incorporates ddNTPs at a greater rate". The Examiner references page 247 of McGuigan as support for the conclusion. However, a closer look at this section suggests otherwise.

In the section cited by the Examiner, McGuigan found that "Sequenase produced fingerprints that are slightly stronger and more even than the fingerprints obtained with reverse transcriptase." Applicants note that here, McGuigan apparently was comparing results obtained using a "Sequenase + manganese" recipe from that of a "reverse transcriptase + magnesium" recipe. From that discussion, Applicants assert that it is unclear whether the better fingerprint results were a result of the use of Sequenase or manganese, or was it a combination of both. In addition, Applicants contend that "a slightly stronger and more even" fingerprint does not necessarily mean a greater incorporation rate (see below).

Applicants note that McGuigan, in the section, also states, "Tabor and Richardson discovered that substituting Mn^{2+} for Mg^{2+} reduces the discrimination against dideoxynucleotides for T7 DNA polymerase". However, Applicants submit that the effect of manganese in reducing the discrimination for dideoxynucleotides, as compared to deoxynucleotides, should not be confused with our invention. Applicants submit that "reducing the discrimination" could be achieved by either an increased rate in incorporating ddNTPs, or a decrease in the rate of incorporating dNTPs. Tabor and Richardson demonstrate that, T7 DNA polymerase incorporates deoxynucleotides

at a much slower rate in the presence of manganese, as compared to in the presence of magnesium (Figure 1). Although they demonstrate that when both dideoxynucleotides and deoxynucleotides are present, manganese increases the relative incorporation of dideoxynucleotides by T7 DNA polymerase, as measured by incorporation ratio of deoxynucleotide to dideoxynucleotide (Table 1), they never measured or discussed the true rate of incorporation of the dideoxynucleotides. See S. Tabor and C.C. Richardson, Proc Natl Acad Sci U S A. 86(11):4076-80, 1989 (cited by the Examiner on page 7 of Office action).

It is worth noting that the references of McGuigen and Tabor and Richardson all utilize based-labeled nucleotides, and these behave differently from terminal phosphate-labeled nucleotides, at the presence of manganese. Applicants have demonstrated in the current application that the incorporation rate of base labeled nucleotide actually drops in the presence of manganese, as compared to magnesium (Example 8 and Figure 3). On the contrary, the incorporation rate of terminal phosphate-labeled nucleotide increases quite dramatically in the presence of manganese, as compared to magnesium

Applicants submit that a skilled person in the art, considering Hardin, McGuigan in light of Tabor and Richardson, could not have reached the conclusion that at the presence of manganese, “the polymerase incorporates ddNTPs at a greater rate”.

Claims 8-10 are also rejected under 35 U.S.C. §103(a) as being unpatentable over Hardin in view of McGuigan et al., further in view of Tabor and Richardson. Applicants respectfully disagree.


Applicants submit that as discussed above, the combination of Hardin and McGuigan is improper and does not render obvious claim 1. Applicants assert that in as much as claim 1 is patentable, the dependent claims 8-10 are also novel and non-obvious.

Applicants are also filing herewith an Information Disclosure Statement providing the Examiner with copies of the references cited on the Supplementary European Search Report dated November 8, 2007, which issued on the corresponding European patent application.

Early and favorable consideration is respectfully requested.

Respectfully submitted,

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